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EXAMINER	
NATARAJAN, MEERA	
ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,428	MANDELBOIM ET AL.	
	Examiner	Art Unit	
	MEERA NATARAJAN	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12,15-19,23,24,27,31-35 and 39* is/are pending in the application.

4a) Of the above claim(s) *23,24,27,31-35 and 39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 8-10, 12, 15, 16 and 19* is/are rejected.

7)☒ Claim(s) *6, 7, 17 and 18* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 May 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, Claims 1-10, 12 and 15-19 in the reply filed on 07/01/2008 is acknowledged. The traversal is on the ground(s) that the reference, Mandelboim et al., cited in the restriction requirement (mailed 04/01/2008) "relates to the background of the present invention and does not show all the details of the present invention which extend throughout the four groups". This is not found persuasive because as stated in the restriction requirement, Mandelboim et al. teach functional fragments of NKp44, NKp30, and NKp46. Mandelboim disclose the fragments of these lysis receptors, NKp44, NKp30, and NKp46, are capable of binding to a ligand expressed on the surface of the target cell. Mandelboim et al. show that NKp44 and NKp46 bind to hemagglutinin, a sulfated polysaccharide-binding protein. Therefore, the reference does in fact teach all the details of Claim 1 and the requirement is still deemed proper and is therefore made FINAL.

2. Claims 23, 24, 27, 31-35, and 39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 07/01/2008.

3. After further consideration, the species requirement for "NCR" is withdrawn and all species, NKp44, NKp30, and NKp46 will be examined.

4. Claims 1-10, 12, and 15-19 will be examined on the merits.

Specification

5. Applicant is invited to amend the first line of the specification to indicate the priority to PCT/IL04/01081 and provisional application 60/524,648.

Claim Objections

6. Claim 6 is objected to because of the following informalities: Claim 6 recites "a fragment of the D2 domain of NKp46 *is* selected from SEQ ID NO:1 and SEQ ID NO:2". The term "is" makes the claim language confusing. Examiner proposes deleting the word "is" to make the claim language clearer and similar to that of claim 17.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-5, 9, 10, 12, 15 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated peptide fragment of natural cytotoxicity receptors (NCR) of natural killer (NK) cells, wherein the peptide is a fragment of the D2 domain of NKp46 selected from SEQ ID NO: 1 and 2, a fragment of NKp30 selected from SEQ ID NO: 3 and 4, or a fragment of NKp44 comprising SEQ ID NO:5, said peptide fragments capable of binding to a membrane-associated biomolecule of a tumor cell, the biomolecule comprising at least one sulfated polysaccharide, said biomolecule serving as the binding site of the NCR mediating the

lysis of tumor cells by NK cells, with the proviso that said peptide is other than a full length NCR polypeptide or an isolated NCR extracellular domain, does not reasonably provide enablement for ***any*** isolated peptide fragment of a natural cytotoxicity receptor (NCR) of natural killer (NK) cells, ***active fragments, analogs or derivatives thereof***, the peptide fragments capable of binding to a membrane-associated biomolecule of a tumor cell, the biomolecule comprising at least one sulfated polysaccharide, said biomolecule serving as the binding site of the NCR mediating the lysis of tumor cells by NK cells, with the proviso that said peptide is other than a full length NCR polypeptide or an isolated NCR extracellular domain . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

9. In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

10. The claims are broadly drawn to a natural cytotoxicity receptor of natural killer cells, analogs or derivatives thereof and fragments as small as 2 amino acids. The instant specification only provides teachings for specific fragments of NKp44, NKp30, and NKp46 comprising SEQ ID NOs: 1-5, which are capable of binding to a membrane-associated biomolecule of a tumor cell. The specification does not define the peptide fragments by function related to structure and therefore it cannot be determined how one would further limit the genus of claimed fragments which met the functional features of the claim. The specification does provide teachings to enable one of ordinary skill in the art to determine which fragments (specifically which residues) of NKp44, NKp30, and NKp46 will be active fragments which are capable of binding to a membrane-associated biomolecule of a tumor cell. In addition, the specification defines derivatives to be “a peptide having various changes, substitutions, insertions, and deletions so long as the peptides retain binding activity" (see p.5). The specification also states the following on page 14: “An "analog" of a molecule is a homologous molecule from the same species or from different species. The amino acid sequence of an analog or derivative may differ from the specific molecule, e.g. the NKp46, NKp3O or NKp44 receptors, used in the present invention when at least one residue is deleted, inserted or substituted.” This broad definition reads on every residue being deleted or substituted or a number of residue insertions resulting in a completely different molecule. The specification does not provide any teaching on which residues are important to retain binding activity and which residues can be deleted, inserted, or substituted. In addition, Claims 2-4 broadly read on fragments “less than about 50”

which would read on fragments as small as 2 amino acids and fragments “about 7” or “about 8".

11. Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al, Journal of Cell Biology Vol 111 November 1990 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252).

12. Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin (Schwartz et al, Proc Natl Acad Sci 1987). Removal of the amino terminal histidine of glucagon substantially decreases the ability of the molecule to bind to its receptor and activate adenylate cyclase (Lin et al Biochemistry 1975).

13. These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein. The results of the construction of synthetic proteins remain very unpredictable as Burgess et al, Lazar et al, Schwartz et al, Lin et al conclusively demonstrate.

14. Therefore undue experimentation would be required to support the broad scope of the claims in order to determine what fragments of NKp46, NKp30, and NKp44 would be capable of binding to a membrane-associated biomolecule of a tumor cell and mediate the lysis of said tumor cells by NK cells.

15. Claims 1-5, 9, 10, 12, 15 and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

16. Applicants claim an isolated peptide fragment of a NCR of NK cells, active fragments, analogs or derivatives thereof. Applicants' specification does not adequately describe or evidence all fragments, analogs, or derivatives thereof . Applicants seem to only be in possession of specific fragments of NKp44, NKp30, and NKp46 comprising SEQ ID NOs: 1-5 (Claims 6-8 and 17-19).

17. "Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was 'ready for patenting' such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention", see Official Gazette, 1242 OG 172, January 30, 2001.

18. Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 115).

19. The claims are broadly drawn to a natural cytotoxicity receptor of natural killer cells, analogs or derivatives thereof and fragments as small as 2 amino acids. Specifically, Claims 2-4 broadly read on fragments as small as “about 7 or 8” or “less than about 50” which would read on 2 amino acids. The instant specification only provides teachings for specific fragments of NKp44, NKp30, and NKp46 comprising SEQ ID NOs: 1-5, which are capable of binding to a membrane-associated biomolecule of a tumor cell. The specification does not define the peptide fragments by function related to structure and therefore it cannot be determined how one would further limit the genus of claimed fragments which met the functional features of the claim. The specification does not provide adequate information regarding which specific residues of a natural cytotoxicity receptor of natural killer cells are important for binding to a membrane-associated biomolecule of a tumor cell.

20. In addition, the specification defines derivatives to be “a peptide having various changes, substitutions, insertions, and deletions so long as the peptides retain binding

activity" (see p.5). The specification also states the following on page 14 : "An "analog" of a molecule is a homologous molecule from the same species or from different species. The amino acid sequence of an analog or derivative may differ from the specific molecule, e.g. the NKp46, NKp3O or NKp44 receptors, used in the present invention when at least one residue is deleted, inserted or substituted." This broad definition reads on every residue being deleted or substituted or a number of residue insertions resulting in a completely different molecule. The specification does not provide any teaching on which residues are important to retain binding activity and which residues can be deleted, inserted, or substituted. In addition, Claims 2-4 broadly read on fragments as small as "about 7" or "less than about 50" which would read on 2 amino acids and therefore would not be enabled as capable of binding to a membrane-associated biomolecule of a tumor cell. The skilled artisan cannot envision the detailed structure of each and every molecule that could possibly be considered "active fragments, analogs or derivatives thereof" and conception is not achieved until reduction to practice has occurred. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The product itself is required. Applicants have not fully described fragments and all the variants embraced by the terms "active fragments, analogs or derivatives thereof" with sufficient particularity such that one skilled in the art would recognize that the Applicants had possession of the claimed invention. See Fiers v. Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016.

21. Furthermore, In The Reagents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412), the court held that a generic statement, which defines a genus by only their functional activity, does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". The specification provides insufficient evidence to support the generic claims.

Claim Rejections - 35 USC § 102

22. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

23. Claims 1-5, 8-10, 12, and 15, 16, and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Mandelboim et al. (WO/2002/008287 published 01/31/2002).

24. The Claims are drawn to an isolated peptide fragment of a natural cytotoxicity receptors (NCR) of natural killer (NK) cells, wherein the peptide is a fragment of the D2 domain of NKp46 selected from SEQ ID NO: 1 and 2, a fragment of NKp30 selected

from SEQ ID NO: 3 and 4, or a fragment of NKp44 comprising SEQ ID NO:5, said peptide fragments capable of binding to a membrane-associated biomolecule of a tumor cell, the biomolecule comprising at least one sulfated polysaccharide, said biomolecule serving as the binding site of the NCR mediating the lysis of tumor cells by NK cells, with the proviso that said peptide is other than a full length NCR polypeptide or an isolated NCR extracellular domain and a pharmaceutical composition comprising said peptide fragments.

25. Mandelboim et al. teach NKp46, NKp30, NKp44 or a functional fragment thereof capable of binding to hemagglutinin (HA) of Influenza virus, a sulfated polysaccharide-binding protein, and the hemagglutinin-neuraminidase (HN) of parainfluenza virus, and that binding of NKp44 and NKp46 to these viral proteins is required for lysis of cells expressing the corresponding glycoproteins (see last paragraph p.2 – top p.3). The target recognition segment is derived from NKp46 and preferably comprises at least one of domains 1 and 2 of the NKp46 molecule, more preferably both domains 1 and 2 (see p. 3, 2nd full paragraph and claims 5-7). Mandeloboim et al. disclose the peptides can be targeted to cells derived from solid as well as non-solid tumors, particularly malignant tumors and can be used to treat pathological conditions in a subject (see p. 4, 4th paragraph and p.6). Mandeloboim et al. teach fragments about 100 and about 120 contiguous amino acids (see attached alignments which teach peptides with 117 and 135 amino acids). Mandeloboim et al. also disclose a functional fragment to be "any nucleotide or amino acid subset of the molecule" (see p.17, 2nd paragraph). This definition would broadly read on fragments about 7 to about 120 contiguous amino

acids, about 8 to about 100 contiguous amino acids, and less than about 50 contiguous amino acids. Mandeloboim et al. also teach a fragment of NKp44 having SEQ ID NO:5 (see attached alignment for NKp44). The fragment taught by Mandeloboim et al. is 244 contiguous amino acids which is less than the 304 amino acids of SEQ ID NO:5 and is therefore considered a fragment. Although Mandeloboim et al. is silent in regards to specific membrane-associated biomolecules which the peptide fragments are capable of binding to, Mandeloboim et al. teach 100% identity to the SEQ ID NOs claimed. Therefore it would be inherent that the peptide fragments taught by Mandeloboim et al. would function in the same manner and bind to heparin, heparan sulfate and dermatan sulfate. The reference teaches each and every limitation of the claims.

Conclusion

26. Claims 1-5, 8-10, 12, 15, 16, and 19 are rejected.

27. Claims 6-7 and 17-18 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

28. No Claim is allowed.

29. Any inquiry concerning this communication or earlier communications from the examiner should be directed to MEERA NATARAJAN whose telephone number is (571)270-3058. The examiner can normally be reached on Monday-Thursday, 9:30AM-7:00PM, ALT. Friday. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MN

/Larry R. Helms/
Supervisory Patent Examiner, Art Unit 1643